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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/598,546	06/04/2007	Romi Barat Singh	RLL-499US	7158

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Ranbaxy Inc.
Intellectual Property Department
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EXAMINER	
MATTISON, LORI K	
ART UNIT	PAPER NUMBER
1619	

NOTIFICATION DATE	DELIVERY MODE
02/18/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/598,546	SINGH ET AL.	
	Examiner	Art Unit	
	LORI MATTISON	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *13-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/22/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-18 are pending in the current application, of which claims 1-12 are being considered on their merits. Claims 13-18 are withdrawn from consideration at this time.

Election/Restrictions

Applicant's election without traverse of Group 1, claims 1-12, in the reply filed on 11/22/2010 is acknowledged. Claims 12-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Examination on the merits will commence on claims 1-12, ONLY.

The restriction is deemed proper and is made FINAL.

Specification

The abstract is objected to because it is not in an acceptable format. Applicant has submitted the face page of the international publication in lieu of an abstract. This face page contains additional text. The abstract of the disclosure must commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Claim Rejections - 35 USC § 112

Claims 3-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Instant claim 3 is unclear because the metes and bound of the claim can not be determined. It is unclear whether it is optional to mix the granules with excipients AND form a solid dosage for, or whether it is only optional to mix the granules with the excipients.

Clarification is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 2004/010998 (AMIDON, 2003; supplied by Applicant) in view of WO 1997/27198 (ARZENO, 1997), DRUG MONITOR (See PTO-892 MAILED on 09/17/2010), HANCOCK (See PTO-892

MAILED on 09/17/2010), US Patent No. 6,660,303 (STANIFORTH, 2003), US Patent No. 5,427,799 (VALENTINE, 1995) and as evidenced by US Publication No. 2007/0129385 (SHARMA, 2005) and the definition of crystallization by the Encyclopedia Britannica as archived on 4/18/2008.

Claim Summary: The claims are generally drawn to a method of preparing a solid dosage form of amorphous valganciclovir into a capsule or a tablet in a dry process. The method comprises the steps of mixing amorphous valganciclovir with an excipient, roller compacting and milling.

Table 3 of Example 3 of AMIDON discloses a sustained release tablet that was formed by compression in a tabletting machine after all dry reagents were mixed (i.e. the tablet was formed via direct compression in a dry process; paragraphs 85 and 117; instant claim 7). No "wet" reagents were used (i.e. the process was a dry process; paragraph 117). The composition utilized in the process comprises the lubricant, magnesium stearate; the glidant, colloidal silicon dioxide; the disintegrant, hydroxypropylmethylcellulose; and the binder, pregelatinized starch (instant claims 2 and 9-12). AMIDON teaches that valganciclovir hydrochloride is a one of the water soluble active pharmaceutical agents which may be utilized in the tablet (paragraph 34). AMIDON teaches that analogous salts of the water soluble active agents may also be substituted into the tablet (paragraph 34). AMIDON teaches that other conventional excipients known in the art can be included in his invention (paragraph 94). AMIDON teaches that the type of starch utilized in the method must be a pregelatinized starch which is more flowable and directly compressible than unmodified starches (paragraph 58). Thus, AMIDON implicitly teaches that flowability and compressibility of the excipients of his invention are important.

AMIDON does not teach the valganciclovir hydrochloride is amorphous as set forth by instant claim 1; inclusion of microcrystalline cellulose as set forth by instant claim 8; steps of mixing amorphous valganciclovir hydrochloride with pharmaceutical excipients, compacting the mixture by roller compactor, milling into granules, and then forming into a solid dosage form which is a capsule or a tablet as set forth by instant claims 3-6.

ARZENO teaches 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propyl L-valinate hydrochloride (i.e. valganciclovir hydrochloride; page 17, lines 25-30). ARZENO teaches that the goals of the invention are to 1) provide products that are of value as anti-viral agents with improved absorption (abstract). While not explicitly stated that the method taught by ARZENO embraces amorphous as well as crystalline valganciclovir, it is observed that Example 6 of ARZENO discloses the process of forming valganciclovir hydrochloride by attaching the hydrochloride ion to the N-CBZ-monovalinate-monobenzyl-ganciclovir through use of a palladium hydroxide catalyst (page 48, last paragraph). ARZENO teaches that the reaction is permitted to go to completion, indicating that valganciclovir hydrochloride was formed, and mixture was filtered and stripped to a low volume (page 48, last paragraph). Water was added and the solution was stripped again to remove the methanol (page 48, last paragraph). Isopropanol was added (thus creating a water and isopropanol mixture) was added and this initiated crystallization (page 48, last paragraph). As evidenced by the Encyclopedia Britannica, crystallization is a purification technique in which solids precipitate from a saturated solution (page 2, paragraphs 1-3). This is distinguished from precipitation which is a process in which an insoluble compound is formed by a chemical reaction (page 2, paragraph 4). Thus, ARZENO teaches that a solid was formed (page 48, last paragraph). More isopropyl was added and the

mixture was stirred, cooled, filtered and dried (page 49, paragraph 1). Similarly, as evidenced by SHARMA, amorphous valganciclovir is formed by reacting N-benzyloxycarbonyl-L-valinate ester of ganciclovir with hydrochloric acid, dissolving the residue in an organic solvent (which may be isopropanol) and removing the solvent to achieve amorphous valganciclovir hydrochloride (Sharma, paragraphs 20 and 21). Therefore, the examiner reasonably concludes that ARZENO teaches amorphous valganciclovir unless Applicant can provide evidence to the contrary.

DRUG MONITOR teaches that valganciclovir has an absolute bioavailability of 60% (page 2, paragraph 1). Thus, approximately 40% of an administered dose of drug is not available to achieve a therapeutic effect. DRUG MONITOR further teaches that to increase the bioavailability of valganciclovir hydrochloride (i.e. Valcyte) and increase peak drug serum levels, valganciclovir hydrochloride (i.e. Valcyte) is administered with high fat food (page 2, paragraph 1). Thus, DRUG MONITOR teaches that there was a known problem in the art with regard to the bioavailability of valganciclovir that members in the field were endeavoring to solve.

HANCOCK teaches the characteristic and significance of the amorphous state of pharmaceutical systems (title). HANCOCK teaches that the amorphous state of pharmaceutical drugs can lead to enhanced dissolution and bioavailability (page 2, column 1, paragraph 1).

STANIFORTH teaches the state of the art of direct compression. STANIFORTH teaches that in tabletting, a tablet is formed b pressure being applied on the lower and punches (column 1, lines 20-40). The ability of materials utilized in tabletting to flow freely into the die is important in order to ensure that there is uniform filling of the die and a continuous movement of

the material from the source material (column 1, lines 20-40). Lubricity of the material is critical (column 1, lines 20-40). The materials to be compresses must also be free-flowing, and possess sufficient cohesiveness to ensure the dosage from remains intact (column 1, lines 20-30). In direct compression the drug must have the requisite crystalline structure and physical characteristic required for formation of a pharmaceutically acceptable tablet (column 2, lines 15-20). However, most drugs have none or only some of the required properties thus one or more excipients can be included to make the direct compression method applicable to drugs which do not posses the requisite physical properties (column 1, lines 40-50; column 2, lines 20-30). Microcrystalline cellulose when compared to other directly compressible excipients is generally considered to exhibit superior compressibility and disintegration properties (column 2, lines 45-45).

VALENTINE teaches a method for forming sustained release compositions (title). The method involves the steps of mixing an active ingredient, xanthan gum, and other excipients (column, lines 60-end). The formulation is compacted by roller compacting, ground (i.e. milled) to reduce the particle (i.e. granule) size, and filled in a final capsule form (column 7, lines 1-10) or the pre-blend is compressed into a final tablet dose form after a lubricant like stearic acid is added to assist in the tabletting process (column 7, lines 1-10). VALENTINE teaches that "any other pharmaceutical or drug having a beneficial effect on the body when released to the gastro-intestinal tract in a slow or sustained manner" may be utilized in her invention (column 5, lines 30-45).

The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. 398, 127 S. Ct. 1727, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a

conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit.

Exemplary rationales that may support a conclusion of obviousness include:

(A) Combining prior art elements according to known methods to yield predictable results;
(B) Simple substitution of one known element for another to obtain predictable results;
(C) Use of known technique to improve similar devices (methods, or products) in the same way;
(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
(E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

In KSR International Co. v. Teleflex Inc.,, 82 USPQ2d 1385, 1397 (U.S. 2007), the Supreme Court has also held that when there is market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person has good reason to pursue known options within his or her technical grasp. Under these conditions, "obviousness to try" such options is permissible.

Note that the above list of rationales provided is not intended to be an all-inclusive list. Other rationales to support a conclusion of obviousness may be relied upon by Office personnel.

With regard to instant claim 1, at least rationales (A and C) of KSR International Co. v. Teleflex Inc. may be employed. It would have been prima facie obvious to a person of ordinary

skill in the art at the time the invention was made to have modified the method taught by AMIDON by substituting the active agent taught by AMIDON with the amorphous valganciclovir hydrochloride taught ARZENO because AMIDON teaches that valganciclovir hydrochloride is a suitable active agent for use in the sustained release tablet of the invention. One would have been motivated to select amorphous valganciclovir hydrochloride for use in the invention because orally delivered valganciclovir hydrochloride has a known problem with bioavailability, artisans in the field were endeavoring to find ways to improve the bioavailability of the drug, and amorphic pharmaceutical drugs state may have enhanced dissolution and bioavailability as taught by the combined teaching of DRUG MONITOR and HANCOCK. One would have had a reasonable expectation of success based upon the teachings by AMIDON that valganciclovir hydrochloride and analogous salts may be included in the tablet of his invention.

With regard to instant claim 8, at least rationale (D) of KSR International Co. v. Teleflex Inc. may be employed. It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to have modified the method taught by AMIDON by substituting adding microcrystalline cellulose to the tablet formulation because the method utilized AMIDON is a direct compression method and microcrystalline cellulose is a direct compression tabletting excipient which is generally considered to exhibit superior compressibility and disintegration properties as taught by STANIFORTH. One would have been motivated to do so in order to improve the flowability and compressibility of the formulation because AMIDON implicitly teaches that flowability and compressibility of the excipients are important to his invention by teaching that the starch utilized in his method must be pregelatinized so that it will be more flowable and directly compressible. One would have had a

reasonable expectation of success based upon the combined teachings of AMIDON, which permit for inclusion of additional pharmaceutical excipients, and the teachings of STANIFORTH, which teach that microcrystalline cellulose is regarded as a superior excipient for direct compression tabletting methods due to its compressibility and disintegration.

With regard to instant claims 3-6, at least rationales (C and D) of KSR International Co. v. Teleflex Inc. may be employed. It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to have modified the method of forming a sustained release tablet taught by AMIDON by utilizing the steps of mixing an active agent with xanthan gum (i.e. excipient), and other excipients, roller compacting, milling into particles and then formulating into tablets or capsules as taught by VALENTINE to produce sustained release dosage forms because AMIDON teaches that the formulation of his invention are sustained release formulations and VALENTINE teaches the above steps as a method to form sustained release capsules and tablets. The above steps are known technique which may be utilized to improve similar methods in the same way (i.e. improving the sustained release composition through use of xanthan gum) and are also a known technique to a improve a similar method ready for improvement to yield predictable results. One would have had an expectation of success based upon the teachings of AMIDON that valganciclovir hydrochloride and its analogous salts are suitable for sustained release compositions (i.e. tablets) implicitly teaching that valganciclovir hydrochloride would benefit from being in a sustained release form and VALENTINE's disclosure that any other pharmaceutical or drug having a beneficial effect on the body when released to the gastro-intestinal tract in a slow or sustained manner may be utilized in her invention.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (In re Opprecht 12 USPQ 2d 1235, 1236, (Fed, Cir. 1989); In re Bode 193, USPQ 12 (CCPA) 1976). In light of the foregoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LORI MATTISON whose telephone number is (571)270-5866. The examiner can normally be reached on 8am-6pm (Monday-Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Wax can be reached on (571)272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LORI MATTISON/
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